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Prospective cohort study exploring the neurodevelopmental outcomes following documented neonatal sepsis in Nepal: study protocol

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ABSTRACT

Introduction Neonatal sepsis, a significant contributor to global neonatal mortality, poses substantial risks to infant health, particularly in low-resource countries like Nepal. Despite its high prevalence, there is a lack of clarity in defining and understanding neonatal sepsis, leading to challenges in diagnosing and managing the condition effectively. The probable impact of neonatal sepsis on long-term neurodevelopmental outcomes, including motor and cognitive delays, remains under-explored in Nepal. The primary objective of this study is to report the prevalence of neurodevelopmental delay in neonates with documented sepsis. The secondary objective is to report significant associations of the same with selected probable risk factors.

Methods and analysis This is a dual-centric prospective cohort study that is ongoing at two hospitals—Paropakar Maternity and Women's Hospital and Siddhi Memorial Hospital in Nepal, over a 2-year period. Neonates diagnosed with sepsis will be assessed using the Developmental Assessment Scale for Indian Infants at 6 months and 1 year, postdiagnosis. Statistical analyses will include prevalence estimation and logistic regression.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Neonatal sepsis is associated with developmental impairment in a subset of survivors. The prevalence of neonatal sepsis is higher in low-resource settings like Nepal. Despite this, there is no data related to impact of neonatal sepsis on neurodevelopmental outcomes among survivors of the same in Nepal.

WHAT THIS STUDY HOPES TO ADD

⇒ The study will provide quality data related to the neurodevelopmental profile of infants who survived neonatal sepsis from hospitals in Nepal.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The information from this study will assist healthcare professionals to provide early diagnosis of neurodevelopmental delay and prompt intervention in survivors of neonatal sepsis in low resources settings.

INTRODUCTION

Neonatal sepsis is defined as 'a systemic condition of bacterial, viral, or fungal (yeast) origin that is associated with haemodynamic changes and other clinical manifestations which results in substantial morbidity and mortality'.[1] Neonatal sepsis has also been referred to as a systemic inflammatory response syndrome that is secondary to infection.[2] Neonatal sepsis occurring within the first 72 hours of life is referred to as early-onset neonatal sepsis (EONS),while that occurring beyond 72 hours is known as late-onset neonatal sepsis (LONS).[3 4]

Neonatal sepsis is generally associated with numerous complications, including multiple organ failures, bronchopulmonary dysplasia, respiratory distress syndrome and neurological complications such as intraventricular hemorrhage, meningitis and periventricular leukomalacia. [5] Among these, developmental delay has been listed as one of the major complications, which often leads to a lifelong burden.[6] The relationship between these two factors may be explained through the infection-triggered inflammation and disruption of normal brain development in neonates after neonatal sepsis leading to neurodevelopmental impairment. The impact of neonatal sepsis on neurodevelopment is based on factors such as the severity of the infection, the timing of treatment and the overall health of the infant.[7]

Despite prior studies reporting neurodevelopmental delay following neonatal sepsis, some issues have not been addressed with clarity.[8–14] In previous research, aspects such as smaller sample size, variation in patient characteristics and reliance on retrospective data may have reduced the accuracy of predicting

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The study is based on clear objectives centered on neurodevelopmental outcomes following neonatal sepsis, employing a thorough methodology to assess prevalence, predictors and associations. The use of Developmental Assessment Scale for Indian Infants, which is tailored to the South Asian context, enables a robust evaluation of motor and cognitive domains. The prospective cohort design enhances data quality and minimises recall bias, allowing for longitudinal analysis of outcomes. Additionally, the dual-center approach enriches participant diversity and generalisability, while strict inclusion and exclusion criteria with a primary focus on neonatal sepsis minimises confounding factors. These strengths together enhance the study's potential to offer valuable insights into the neurodevelopmental impacts of neonatal sepsis.

⇒ Some of the expected study limitations include anticipated loss to follow-up, inadequate resources, unmeasured confounders and varying interpretations of scores during developmental assessment. Addressing these challenges during the course of the study can maximise the study's impact and contribute to understanding neurodevelopmental outcomes following neonatal sepsis. Further, the findings from this study may not be entirely generalisable to cases treated in lower-level settings.

developmental delay. Even though developmental delays in both mental and motor domains were reported in these studies, a thorough assessment using the available mental and motor clusters was not conducted.

This study is especially imperative in countries like Nepal due to several reasons. First, resources in low- and middle-income countries resources are limited, and access to specialised paediatric care is often unavailable during the initial stages. This scarcity exacerbates the challenge of effectively managing neonatal sepsis, potentially leading to adverse neurodevelopmental outcomes. Moreover, the lack of reliable microbiological investigations to aid in diagnosing neonatal sepsis further compounds the issue, as it results in the failure to identify neurodevelopmental impairment early on. This underscores the critical need for comprehensive research to bridge this gap in knowledge and practice. Furthermore, there is a dearth of studies that have investigated these aspects, specifically in Nepal. By addressing these gaps, the study can provide valuable insights into the neurodevelopmental outcomes of neonatal sepsis in the Nepalese context, which would be useful for both clinical practice and public health strategies. Identification of modifiable predictors in this study would also encourage future researchers to come up with intervention studies targeting the reduction in neurodevelopmental delay in infants who are treated for neonatal sepsis.

METHODS AND ANALYSIS

Aim of the study

This study aims to investigate the occurrence of motor and cognitive delays after documented neonatal sepsis in Nepal using the Developmental Assessment Scale for Indian Infants (DASII). Assessment using DASII will enable a detail assessment of several specific clusters related to both mental and motor development.

Objectives of the study

Primary

To estimate the prevalence of neurodevelopmental delay in neonates with documented sepsis after 6 months using DASII.

Secondary

- Estimate the prevalence of neurodevelopmental delay in neonates with documented sepsis after 1 year.
- Evaluate the association between neurodevelopmental delay in neonates with documented sepsis with demographic, socioeconomic and clinical variables, after 6 months and 1 year during follow-up.

Study design and settings

This is a dual-centric, prospective cohort observational study which is currently ongoing at two hospitals in Nepal. These two study sites are Paropakar Maternity and Women's Hospital, Kathmandu, and Siddhi Memorial Hospital, Bhaktapur. Both the centres have level III neonatal intensive care unit and neonatal critical care referral centres in Kathmandu Valley. Three trained paediatricians are in charge of the diagnosis, prevention and treatment of neonatal sepsis at the primary centre (Paropakar Maternity and Children's Hospital). Similarly, two trained paediatricians are in charge of diagnosis, prevention and treatment of neonatal sepsis at the secondary centre (Siddhi Memorial Hospital). Participants who are included will be infants from both centres with the diagnosis of neonatal sepsis. DASII tool will be used by the principal investigator (PI) along with one trained research associate for neurodevelopmental assessment among enrolled infants. The infants will be followed up at 6 months and 1 year after discharge for neurodevelopmental assessment. We will use corrected age for preterm infants who are enrolled in the study. This approach will ensure that developmental assessments are appropriately adjusted for prematurity.

The study questionnaire (study proforma) will include clinical, socioeconomic and demographic variables as well as neurodevelopmental outcomes. Data will be checked independently by two researchers to ensure accuracy. Confidentiality of participants will be maintained through unique identifier number.

Patient and public involvement

Patients and public were not involved in the design, conduct or dissemination plans of this study protocol.

Primary outcomes

Developmental mental quotient (DMeQ), developmental motor quotient (DMoQ) and overall developmental quotient (DQ) at 6 and 12 months.

The scoring criteria for DMeQ and DMoQ will be as follows:

- Average: 85–115.

- Below average: 70–85.
- Overall delay: <70.
  - Mild delay: 50–70.
  - Moderate delay: 30–50.
  - Severe delay: <30.

The overall DQ will be a composite score calculated as the average of DMeQ and DMoQ. The scoring criteria will remain the same as that mentioned above.

Secondary outcomes

Specific clusters within the motor and mental domain at 6 and 12 months including:

- Classification of mental and motor developmental delays:
  - Cluster performance percentile ranks using the DASII tool:
    - <10th percentile: delay.
    - 10th to 25th percentile: below average.
    - 25th to 75th percentile: average.
    - >75th percentile: above average.
- Mental developmental clusters: 10 in number
  - Evaluates areas such as visual and auditory awareness, memory, language, social interaction and cognitive differentiation.
- Motor developmental clusters: 5 in number.
  - Focuses on neck and body control, coordinated movement, locomotion skills and manipulation abilities.

The study aims to comprehensively assess the impact of neonatal sepsis on neurodevelopmental status by refining the developmental outcomes into specific categories and providing precise cutoffs.

Key variables that will be studied for associations with neurodevelopmental impairment include neonatal and perinatal factors, maternal factors, family history, medications and other related factors that may influence the outcomes.

Criteria for patient inclusion

Neonates with documented sepsis attending the two study sites namely, Paropakar Maternity and Women's Hospital and Siddhi Memorial Hospital, will be included in the study. This would include both inborn and out born admissions diagnosed with neonatal sepsis. Both term and preterm infants will be part of the study. The age of diagnosis for inclusion in the study will be within the neonatal period, specifically within the first 28 days of life.

Criteria for patient exclusion

- Neonates having severe life-threatening diseases or conditions unrelated to neonatal sepsis including multiple organ dysfunction syndrome (condition characterised by the failure of multiple organ systems due to systemic illness) or hepatorenal syndrome (renal failure that occurs in the context of severe liver disease).
- Neonates with hypoxic ischaemic encephalopathy grade II or III.
- Neonates with gross congenital malformations (significant structural abnormalities present at birth, such as major heart defects, neural tube defects or severe physical deformities), gross genetic syndromes (major genetic disorders with a significant impact on development, including conditions such as Down syndrome, Turner syndrome or other chromosomal abnormalities) and gross metabolic disorders (severe metabolic conditions affecting overall health and development, such as phenylketonuria, galactosemia or severe inborn errors of metabolism).
- Death of the participant before first follow-up assessment.
- Neonates with birth weight less than 800 g or those who are extremely preterm (less than 28 weeks of gestational age).

Sample size

The sample size calculation was based on a pilot study of 50 patients. The pilot study reported a prevalence of 8% for motor delay and 14% for mental delay. We expect a 10% loss to follow-up and 10% mortality during follow up. The minimum sample size computed with 5% absolute precision and 5 % α error comes to 185 patients. We intend to recruit 500 infants in this study This sample size will enable as to perform additional subgroup analyses related to study outcomes.This total recruitment goal of 500 is contingent on feasibility, logistical constraints, funding and other practical considerations.

Recruitment

The PI and designated research associates will identify potential participants by daily visits to the study institutions. The information will then be conveyed to caregivers using an enrolment sheet. Interested caregivers will undergo rapid screening for eligibility, including providing general information on the child's demographic characteristics and meeting inclusion criteria. Caregivers of eligible children identified during initial screening will review the informed consent form on the same day. Information about the study will be provided in the caregiver's preferred language. All recruitment will be done only after documenting the caregivers' written informed consent to participate in the study.

Definitions

Development is considered delayed when it is more than two SD below the mean in one or more developmental domains. Developmental domains are categorised into (1) receptive and expressive language; (2) gross and fine motor functions; (3) cognition; (4) social and personal development; (5) activities of daily living. These domains correspond to developmental areas outlined in International Classification of Diseases (ICD)-10 and ICD-11. Additional domains like social and personal development and activities of daily living, also known as adaptive

behaviour, were suggested to be considered according to comprehensive neurodevelopmental assessment. Neurodevelopmental delay can be defined as 'atypical central nervous system (CNS) that can occur at any point of life, in-utero through the early developmental period up to 5 years of life', or it may also be defined as 'delays in skill development of infants or young children'.[15 16] Similarly, global developmental delay is defined as 'a significant delay in 2 or more domains affecting children under the age of 5 years'.[17 18] The phrase 'documented sepsis' refers to cases of neonatal sepsis confirmed through specific diagnostic criteria. For culture-negative sepsis, the diagnosis is established when all of the following criteria are met: (1) at least two infection-related clinical manifestations; (2) abnormal white blood cell count, C reactive protein level or procalcitonin level; (3) antibiotics used or intended for ≥5 days; (4) negative blood culture with no or negative cerebrospinal fluid culture; and (5) absence of concurrent focal infections such as pneumonia or necrotising enterocolitis. For culture-positive sepsis, the diagnosis is defined by a positive blood or cerebrospinal fluid culture.[19]

Developmental tool: DASII

This study intends to apply DASII scale for developmental assessment during follow-up which is more appropriate in the South Asian context. The DASII is the Indian modification of the Bayley Scale of Infant Development applicable for 1–30 months of age. The first modification was done in 1970 and the final modification in 1997.[20] DASII consists of 67 and 163 items for motor and mental domains, respectively. Each domain is further divided into five clusters for motor developmental assessment and 10 clusters for mental developmental assessment. The mental developmental assessment is done using 163 items distributed across 10 clusters, including visual awareness, auditory awareness, exploration and manipulation, memory, social interaction, language development, comprehension, understanding relationships, cognitive differentiation and manual dexterity. The motor developmental assessment consists of 67 items categorised into five clusters, covering neck control, body control, coordinated movement, locomotion skills and manipulation abilities.

A preliminary neurodevelopmental intervention initiative, which incorporates developmental evaluation through DASII, an indigenous Indian tool, demonstrated feasibility and potential efficacy for infants and young children who are at risk of developmental disabilities.[21] DMeQ, DMoQ and Composite DQ are reported in the DASII assessment, with an average DQ of 100 and an SD of 15. The cut-off points used for developmental delay/adverse developmental outcomes ranged from 70 to 85.[22]

Follow-up assessment: monitoring

Follow-up assessment of all recruited infants is a crucial part of this study. The primary investigator and designated research associates involved in this study are certified in the usage of the developmental tool. Two of the researchers will be involved in conducting the major part of the assessment in follow-up after 6 months and 1 year. Each neurodevelopmental follow-up assessment will be conducted in designated rooms of both the participating study centres. These rooms are provided specifically for the DASII assessment as per the requirement of neurodevelopmental assessments. The monitoring of follow-up will be done by the primary investigator to ensure accuracy and data quality. The assessment reports will be provided to the caregivers during the second follow-up after completion at 1 year of age. In addition, the necessary information regarding the interpretation of the scores will be provided and explained through the developmental assessment report sheet. During assessments, each enrolled child will be observed and developmental quotient scoring will be done accordingly. After each developmental assessment, motor and mental clusters will be scored, including aspects such as fine and gross motor skills, balance, coordination, cognitive skills, language development, problem-solving, attention, memory and social interaction.

Statistical methods

All statistical analysis will be done using SPSS V.27. We will present descriptive analysis to describe the study sample profile. We will summarise continuous variables as means with SD or as medians with interquartile range (IQR). All categorical variables will be reported as proportions. The prevalence rate of neurodevelopmental delay in neonates with documented sepsis will be calculated, along with its 95% CI. We will use χ^2 test to evaluate the statistical significance of associations between categorical variables and developmental delay. The Student's t-test will be used to assess the statistical significance of association between continuous variables and developmental delay. We will use logistic regression to examine the association between variables that appear significant in bi-variate comparisons mentioned above. The significant associations using multiple logistic regression will be reported by calculating Odds ratio (OR) and their corresponding 95% CI.

Missing data

All participants who withdraw from the study will be documented along with the reasons for the same. The potential influence of missing data on outcomes will be assessed through sensitivity analysis using augmented datasets. Participants dropping out after 6 months will be included in the analysis, and any missing data will be addressed through the imputation of values.

Informed consent

Study personnel will clarify the study details and acquire written informed consent from the caregiver or legal guardian of the child involved in the study.

This will be done before the recruitment of participants. Informed consent will be presented in either English or Nepalese, according to the caregiver's preference. On receipt of signed informed consent, study personnel will furnish the caregiver with a copy of the informed consent document and the original document will be archived for future reference.

Study status

We have recruited 314 participants to the study till date (July 2024). We completed 6 months neurodevelopmental assessment of 205 patients . In addition, we completed 1 year neurodevelopmental assessment in 98 patients.

Ethics and dissemination

The study was approved by the Nepal Health Research Council under the Ministry of Health in Nepal (Ref No. 1545) and the Research Ethics Committee of Amrita Institute of Medical Sciences, Kochi, India (ECASM-AIMS-2022-237). All recruited participants agreed to participate and signed a written consent form after receiving written and oral information about the study. Study findings will be published in peer-reviewed scientific journals and will be presented at national and international conferences.

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Contributors SV: conducted extensive literature reviews to provide a comprehensive understanding of the epidemiology and impact of neonatal sepsis, particularly in low-resource settings like Nepal; collaborated with coauthors to ensure the clarity and coherence of the introduction section, effectively framing the study's objectives within the broader context of neonatal health; provided critical insights into the unique challenges faced by healthcare systems in Nepal in managing neonatal sepsis, highlighting the importance of addressing these challenges through research and intervention strategies. MR: provided overarching leadership throughout the research process; effectively coordinated contributions from all authors, ensuring alignment with research objectives and compliance with ethical standards; contributed insights to the introduction section, framing the study's objectives within the broader landscape of neonatal sepsis research; MR, the corresponding author, is the guarantor of this study protocol. He accepts full responsibility for the integrity of the data, the accuracy of the analysis and the conclusions drawn from the study. RS: made substantial contributions to the methods and analysis section; meticulously detailed the study's design, settings, recruitment process, sample size determination and follow-up assessment protocols; ensured the methodological robustness and reliability of the study's procedures. JC: played a crucial role in defining neurodevelopmental delay; provided comprehensive explanations of the developmental tool (DASII) and elucidated the follow-up assessment process, including monitoring and statistical methods; ensured clarity and accuracy in assessing neurodevelopmental outcomes. SBK: contributed extensively to the literature review within the introduction section; emphasised the study's significance in the Nepalese context and advocated for comprehensive research to address existing knowledge gaps; enriched the background of the study with valuable insights. KS: provided valuable input to the ethical considerations and dissemination section; detailed the approval process from relevant authorities and outlined the plan for disseminating study findings; ensured adherence to ethical standards and guidelines. GBR: offered insights into the practical implications of the study findings; emphasised the importance of tailored information to address neurodevelopmental outcomes in neonatal sepsis cases; provided valuable input on implementing early identification and intervention programs in clinical settings. DS: played a crucial role in the statistical methods section; meticulously detailed the statistical analysis plan, including handling missing data and addressing potential biases in the study design; ensured the validity and reliability of the statistical analyses conducted.

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Competing interests The authors declare no competing interests regarding the publication of this study protocol exploring the neurodevelopmental outcomes following documented neonatal sepsis in Nepal. There are no financial or non-financial interests that could be perceived as potentially influencing the objectivity, integrity or validity of the research conducted or the conclusions drawn from it. All authors involved in the development of this protocol have no affiliations or involvement with any organisations or entities that have a direct or indirect interest in the subject matter discussed in this study. The research is conducted with the sole purpose of advancing knowledge and understanding neonatal sepsis and its impact on neurodevelopmental outcomes, without any external influences or conflicts of interest.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants. The study received approval from the Nepal Health Research Council under the Ministry of Health in Nepal (reference number 1545) and the Research Ethics Committee of Amrita Institute of Medical Sciences, Kochi, India (ECASM-AIMS-2022-237). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; internally peer reviewed.

Data availability statement Data sharing not applicable as no datasets generated and/or analysed for this study. Not applicable.

Author note The study proforma will be included as an online supplemental appendix in this protocol to offer a clear overview of the study.

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